Armed Forces College of Medicine

AFCM

Glomerular disease

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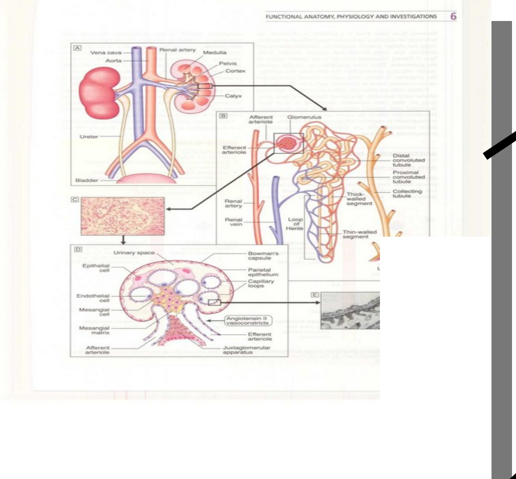
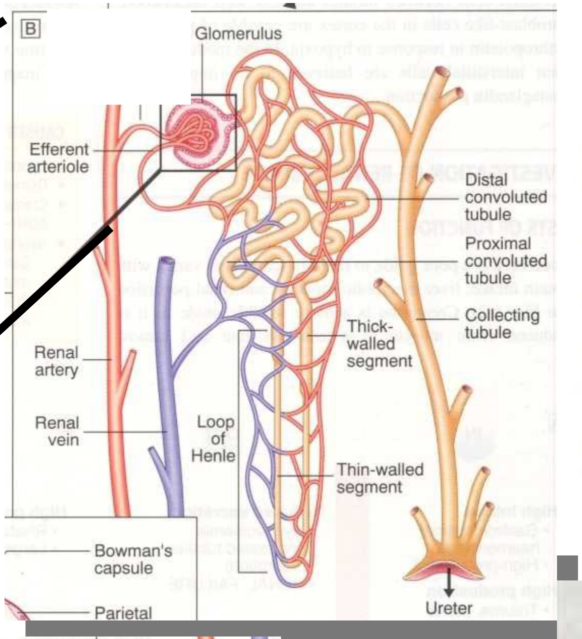
ILO”S

1. To identify the different glomerular syndromes.
2. To differentiate between different glomerular syndromes.
3. To define criteria for each syndrome.
4. To list the main causes of each glomerular syndrome.
5. To analyze the different investigations needed to diagnose different glomerular syndromes.
6. To distinguish different approaches for treatment (details not required).

A pre-reading question
what is the glomerular basement membrane?


FUNCTIONAL ANATOMY, PHYSIOLOGY AND INVESTIGATIONS 6
A
Vena cava
Aorta
Renal artery
Medulla
Pelvis
Cortex
Calyx
Ureter
Bladder
B
Afferent arteriole
Glomerulus
Efferent arteriole
Distal convoluted tubule
Proximal convoluted tubule
Collecting tubule
Thick-walled segment
Renal artery
Renal vein
Loop of Henle
Thin-walled segment
C
D
Urinary space
Bowman's capsule
Epithelial cell
Parietal epithelium
Capillary loops
Endothelial cell
Mesangial cell
Mesangial matrix
Angiotensin II vasoconstricts
Efferent arteriole
Afferent arteriole
Juxtaglomerular apparatus
E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Renal vein
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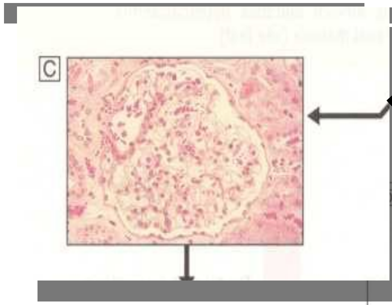
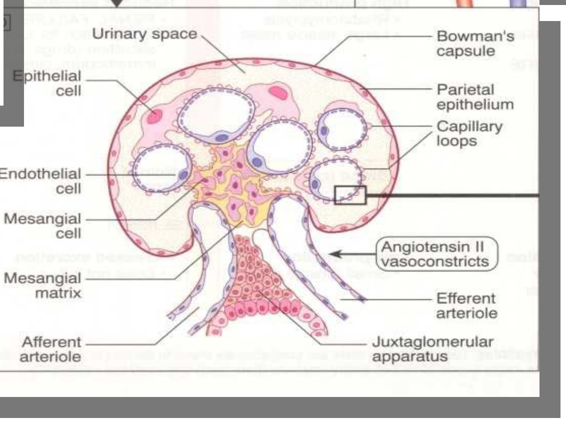
Bowman's capsule
Parietal
Ureter


C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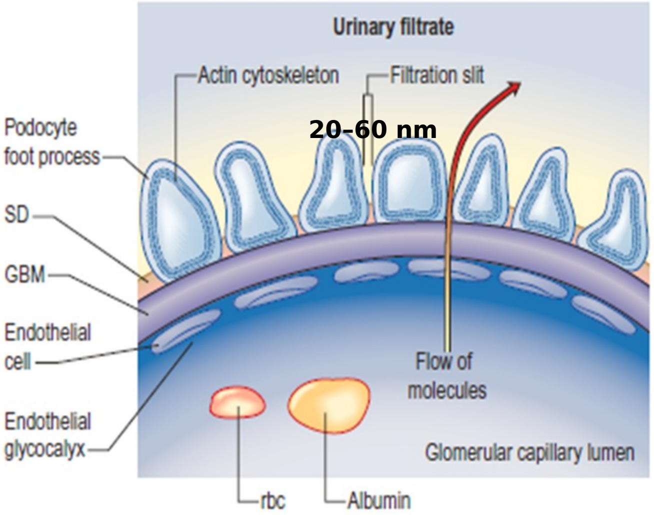
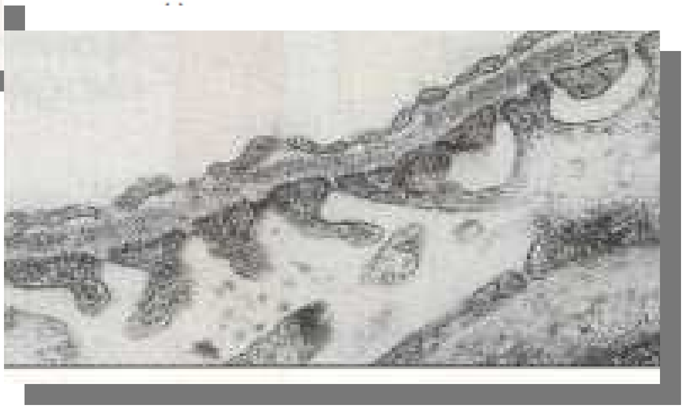
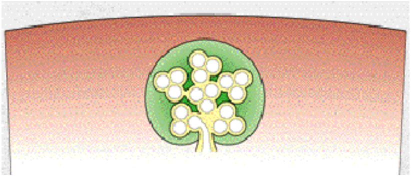

Urinary filtrate
Actin cytoskeleton
Filtration slit
20-60 nm
Podocyte foot process
SD
GBM
Endothelial cell
Endothelial glycocalyx
Flow of molecules
Glomerular capillary lumen
rbc
Albumin

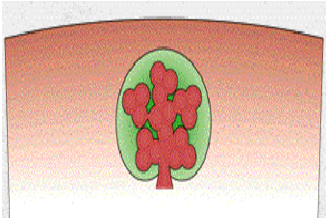


A pre-reading question
what is the histological structure of glomerulus?
Pathological lesion?

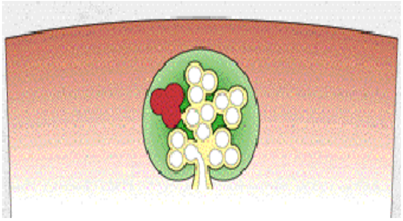
Pathological terms in glomerular disease



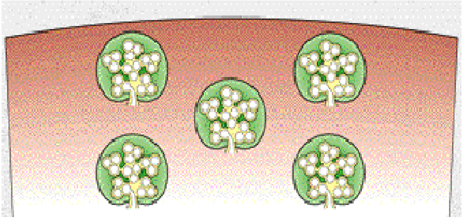
Normal



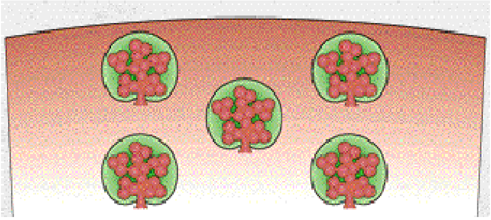
Global
if the whole glomerular tuft is involved



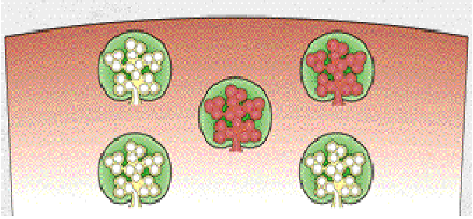
Segmental
only a part of the glomerulus is affected



Normal



Diffuse
most of the glomeruli (> 75%) contain the lesion.

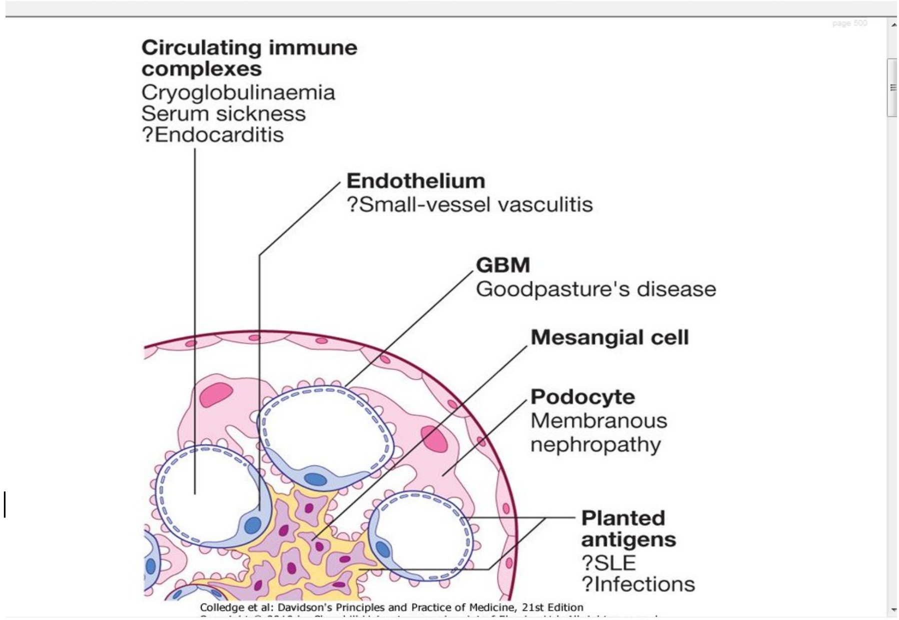


Focal
some but not all the glomeruli contain the lesion.

Target of immunity and autoimmunity in glomerulonephritis

Where antibodies and antigen-antibody (immune) complexes may be seen

- Subepithelial : between podocyte a GBM.
- Intramembranous: within GBM.
- Subendothelial: between endothelium and GBM.
- Mesangial: within the mesangial matrix.



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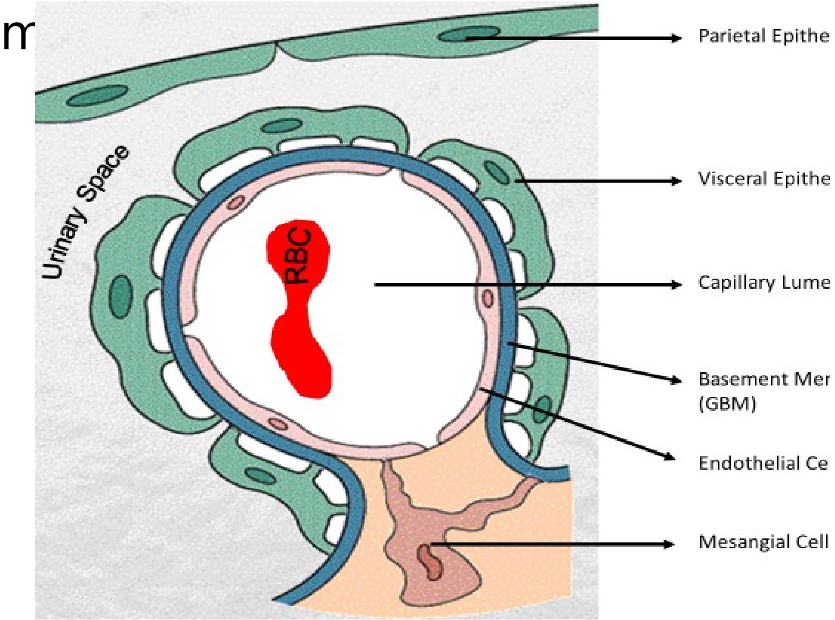
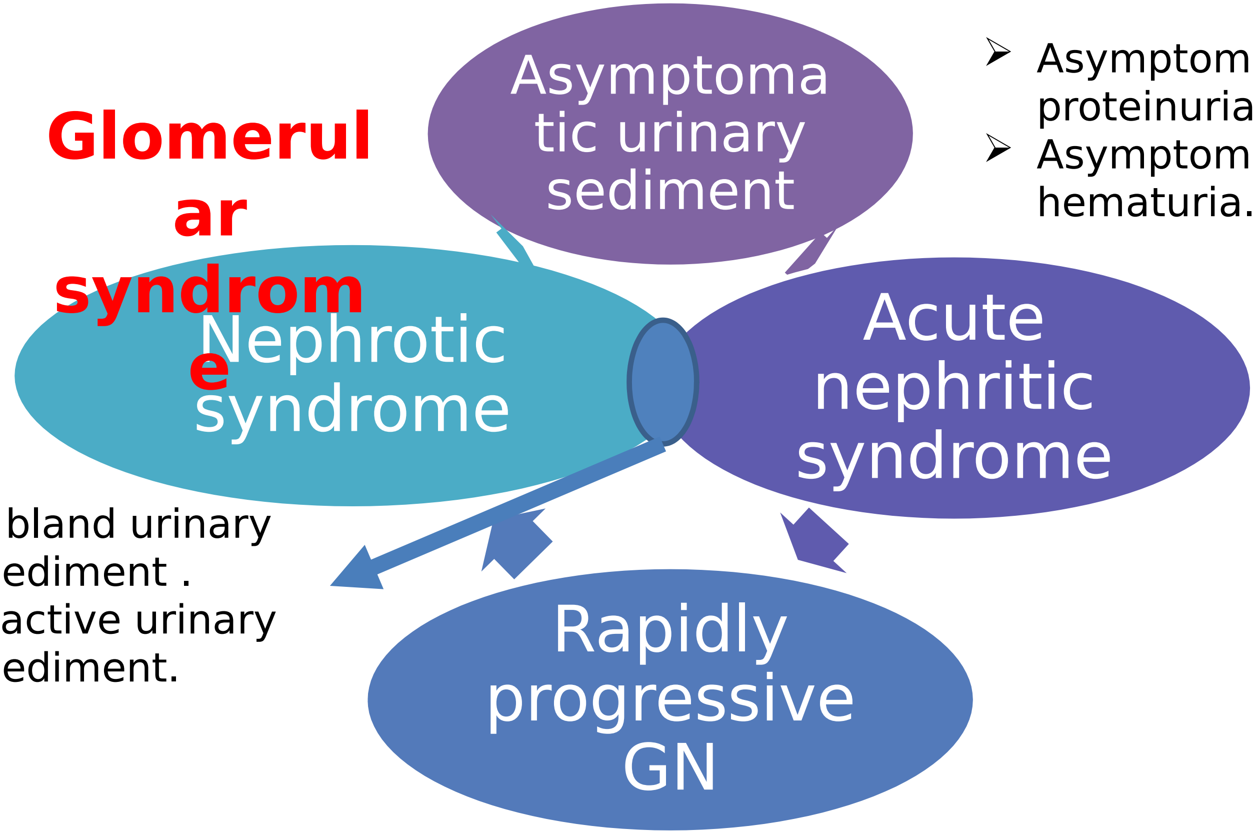


Clinical syndromes associated with glomerular diseases



Glomerular syndrome

Asymptomatic urinary sediment

Nephrotic syndrome

Acute nephritic syndrome

Rapidly progressive GN

- Asymptomatic proteinuria.
- Asymptomatic hematuria.

- With bland urinary sediment .
- With active urinary sediment.

Definition of clinical syndrome

Acute Nephritic Syndrome (ANS)

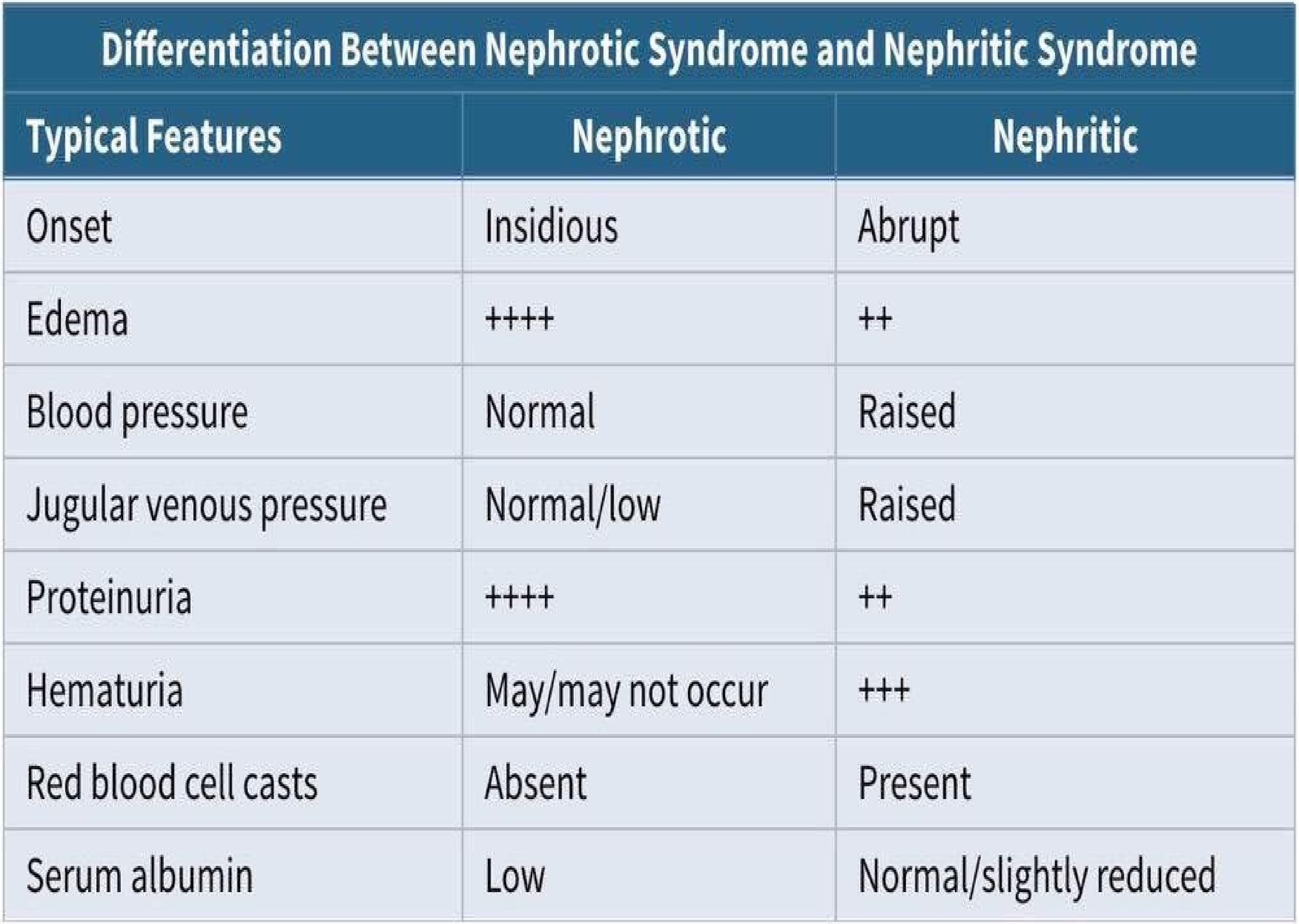
Abrupt onset (days) of:
Hematuria—macroscopic or microscopic (RBC casts)
Hypertension
Oliguria
Edema—moderate
Proteinuria—mild to moderate
Azotemia

Rapidly Progressive Glomerulonephritis (RPGN)

Acute onset of:
Rapidly progressive renal failure (deveoped *within weeks to months* with diffuse glomerular cresent)
Hematuria with RBC casts
Oliguria—variable
Hypertension—unusual
Proteinuria—variable

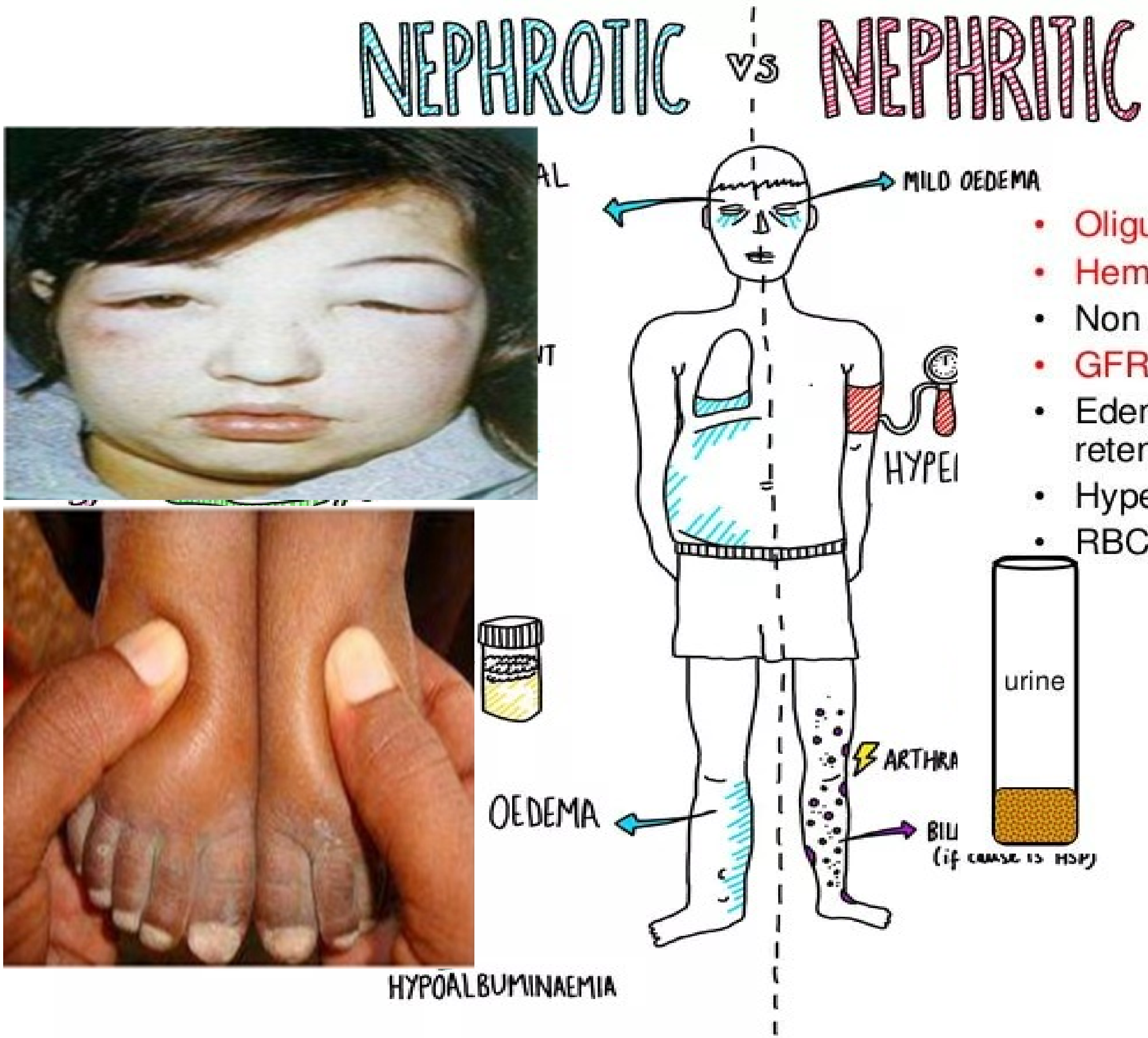
Nephrotic Syndrome(NS)

Insidious onset of:
Proteinuria—>3.5gm/1.7m2
Edema—severe (anasarca)
Hypoalbuminemia
Hyperlipidemia
Lipiduria
Hypercoagulability



Differentiation Between Nephrotic Syndrome and Nephritic Syndrome

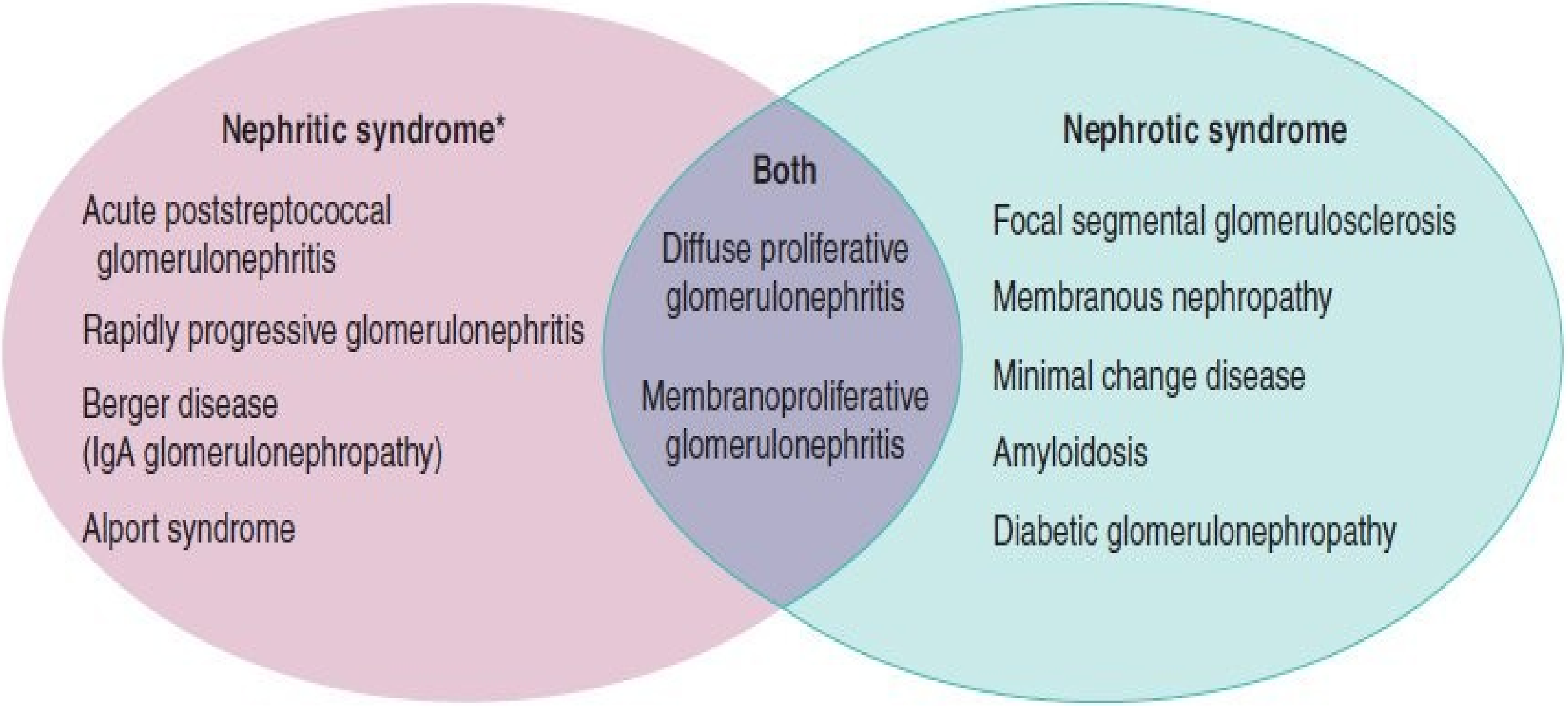
Typical Features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	May/may not occur	+++
Red blood cell casts	Absent	Present
Serum albumin	Low	Normal/slightly reduced



- Oliguria
- Hematuria
- Non selective Proteinuria.
- GFR↓, Cr↑, BUN↑
- Edema (salt and water retention)
- Hypertension
- RBC & Protein casts.

Clinically …….

Glomerular diseases



Nephritic syndrome*

- Acute poststreptococcal glomerulonephritis
- Rapidly progressive glomerulonephritis
- Berger disease (IgA glomerulonephropathy)
- Alport syndrome

Both

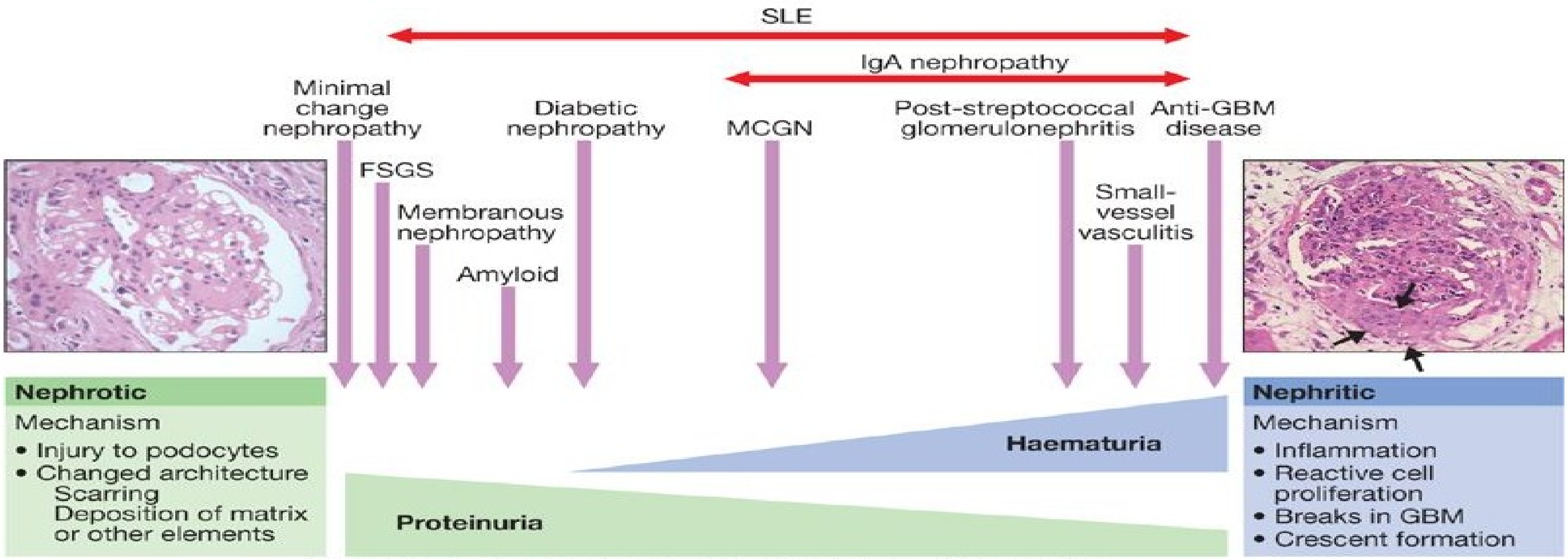
- Diffuse proliferative glomerulonephritis
- Membranoproliferative glomerulonephritis

Nephrotic syndrome

- Focal segmental glomerulosclerosis
- Membranous nephropathy
- Minimal change disease
- Amyloidosis
- Diabetic glomerulonephropathy

*Note that classic nephritic disorders can exhibit nephrotic features.

Differential diagnosis of glomerular diseases



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Diseases presented by either nephrotic and nephritic can be idiopathic or secondary to other causes.

Approach to patient with glomerular diseases

1st

- **Investigation to recognize the glomerular syndrome**
- History taking and examination.
  - **Urinalysis :** RBCs, RBCs cast, proteinuria.
  - **Quantitative urinary protein.** Nephrotic range proteinuria (>3.5 gm/24h), subnephrotic range.
  - **Renal function tests:** blood urea, creatinine, estimated GFR, creatinine clearance.
  - Renal imaging (to differentaite between acute and chronic and to exclude obstructive uropathy)

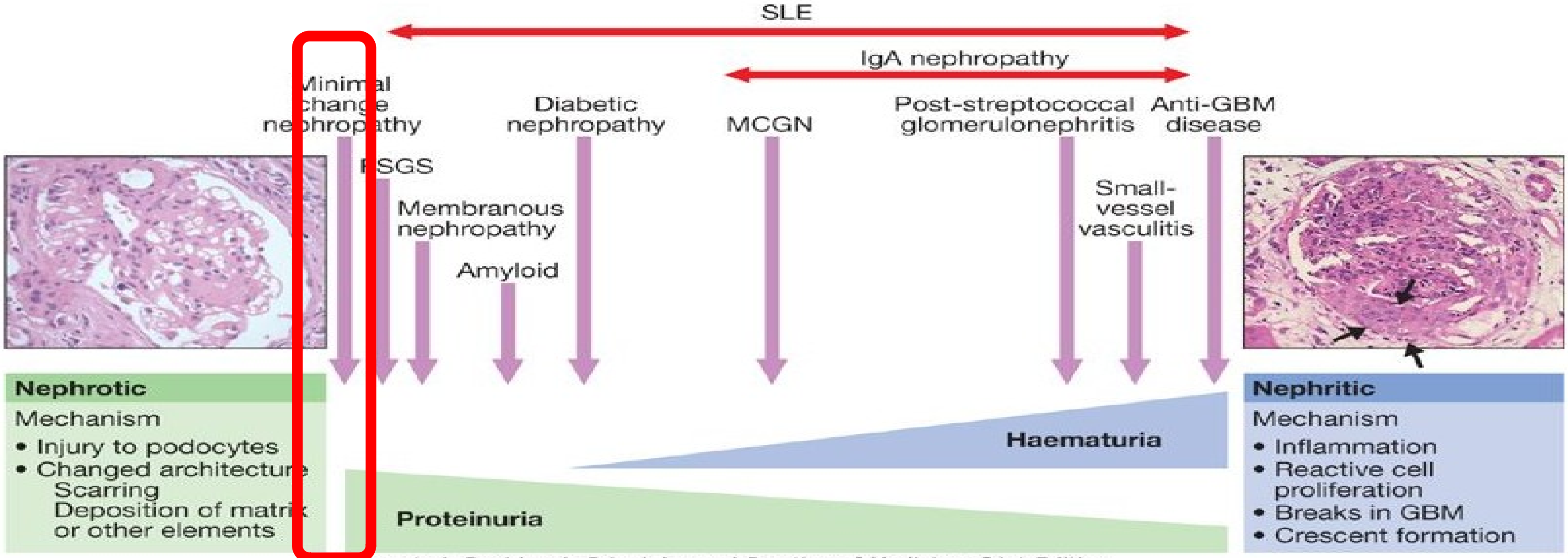
2nd

- **Investigation to recognize histopathological diagnosis**
  - Renal biopsy

3rd

- **Investigation to recognize the underlying causes:**
- ANA (antinuclear antidoy) Anti-ds DNA positive in systemic lupus erythromatosis (SLE).
- C3, C4 (complement) may be comsumed.
- ASOT (anti-streptolysin O titre) positive in post streptococcal GN.
- Viral markers.
- ANCA (antineutrophilic antibody) positive in Wagner granulomatosis.
- Antiglomerular basement membrane (AGBM) positive in Goodpasuture syndrome.

Differential diagnosis of glomerular diseases



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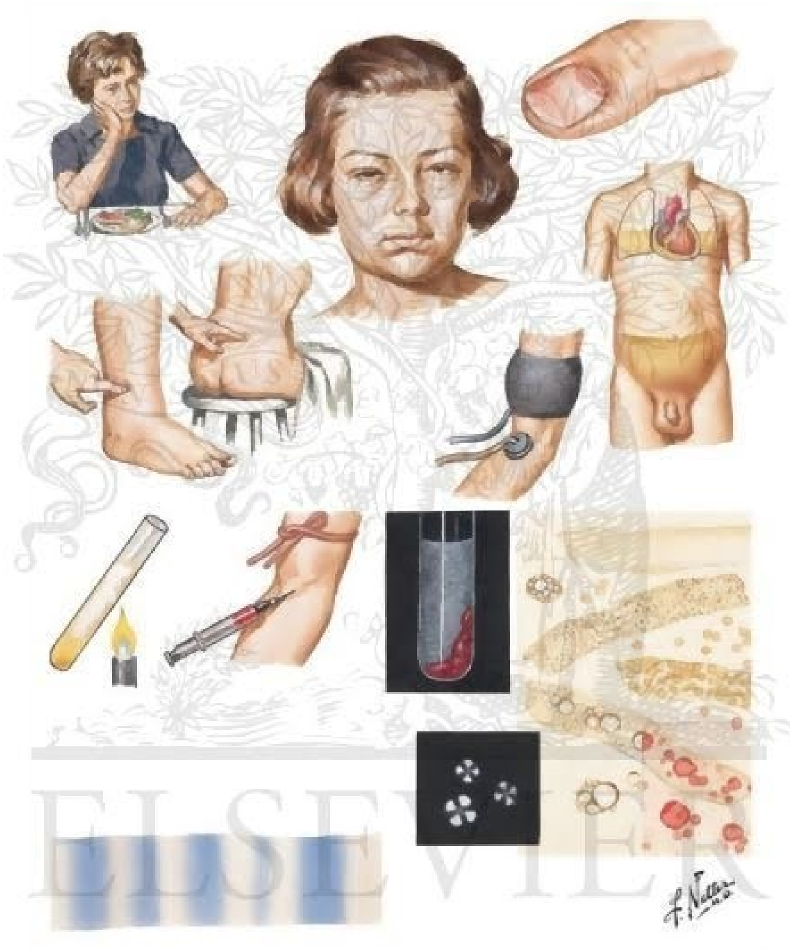
Nephrotic syndrome

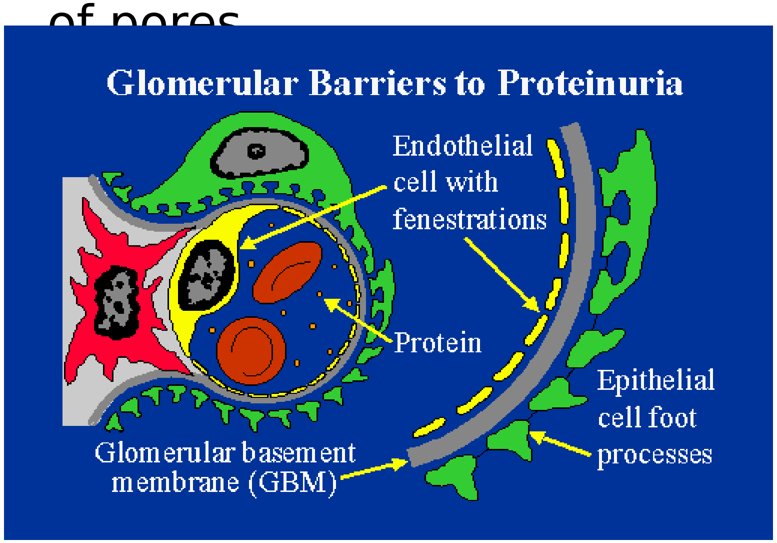


- **Insidious onset of:**
- **Proteinuria—>3.5gm/day/1.7m2 in adult.**
- **Hypoalbuminemia**
- **Edema—severe (anasarca)**
- **Hyperlipidemia , lipiduria**
- **Hypercoagulability**

The mechanism of the proteinuria

Structural damage to the glomerular

An increase in the size and number of pores


Glomerular Barriers to Proteinuria
Endothelial cell with fenestrations
Protein
Epithelial cell foot processes
Glomerular basement membrane (GBM)

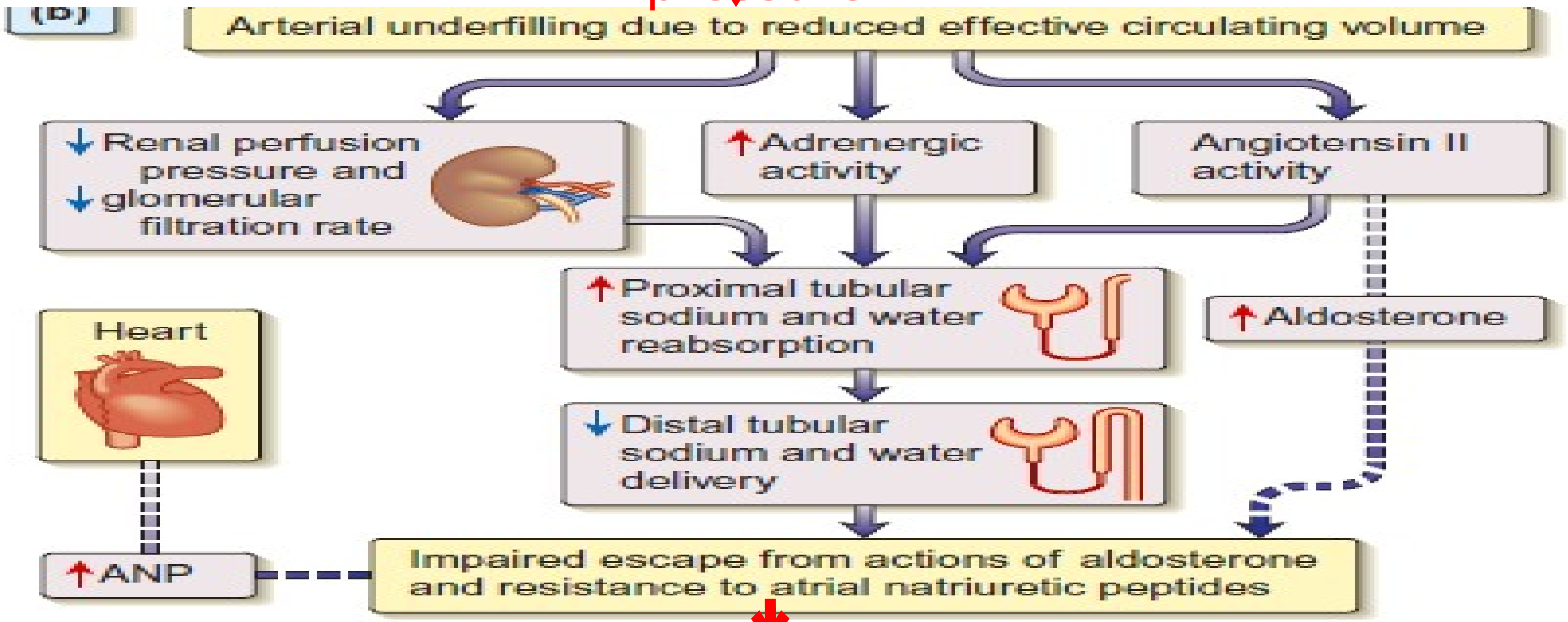
Reduction of Fixed negatively charged protein molecules

appears to be a key factor in the genesis of heavy proteinuria.

Urinary protein loss ≥3.5 g daily cause hypoalbuminemia

Mechanism of edema

hypoalbuminemia → Decreased the oncotic pressure



(b)
Arterial underfilling due to reduced effective circulating volume
↓ Renal perfusion pressure and
↓ glomerular filtration rate
↑ Adrenergic activity
Angiotensin II activity
↑ Proximal tubular sodium and water reabsorption
↑ Aldosterone
Heart
↓ Distal tubular sodium and water delivery
↑ ANP
Impaired escape from actions of aldosterone and resistance to atrial natriuretic peptides

salt & water retension

Hyperlipidaemia
Hypercoagulable state

This increase the cardiovascular risk

The characteristic lipid disorder:

- An increase in the low-density lipoprotein (LDL).
- An increase very-low-density lipoprotein VLDL).
- An increase intermediate-density lipoprotein (IDL).
- No change or decrease in HDL.
- An increase in the LDL/HDL cholesterol ratio.

- Hypercoagulable states predispose to venous thrombosis.
- The hypercoagulable state is due to loss of clotting factors (e.g. antithrombin) in the urine and an increase in hepatic production of fibrinogen

Management

General measures

- *Dietary sodium restriction*
- *Diuretics.*
- Long term anticoagulant in patient with thrombosis.
- Sepsis: Early detection and aggressive treatment of infections.
- ACE inhibitors and/or angiotensin II receptor antagonists.
- Control BP of <130*/80 mmHg.*
- HMG-CoA reductase inhibitor for hyperlipidemia.
- Protein diet = 0.8 gm/kg + gm of protein in urine.

Specific measures

- The aim is to reverse the abnormal urinary protein leak which differ according to the histopathological pattern.

DD of Nephrotic syndrome

Nephrotic syndrome with bland urinary sediment.

Primary glomerular disease.

- Minimal change glomerular lesion
- Focal segmental glomerulosclerosis.
- Membranous nephropathy.
- Amyloidosis
- Diabetic nephropathy.

Nephrotic syndrome with active urinary sediment

- MPGN.
- Lupus nephritis.
- Henoch-Schönlein purpura,
- Mixed essential cryoglobulinemia.

All may be idiopathic or secondary to other diseases

Time for Students’ Questions

students' activity

Enumerate :

causes of Nephrotic syndrome with bland urinary sediment.

Secondary causes of nephrotic syndrome

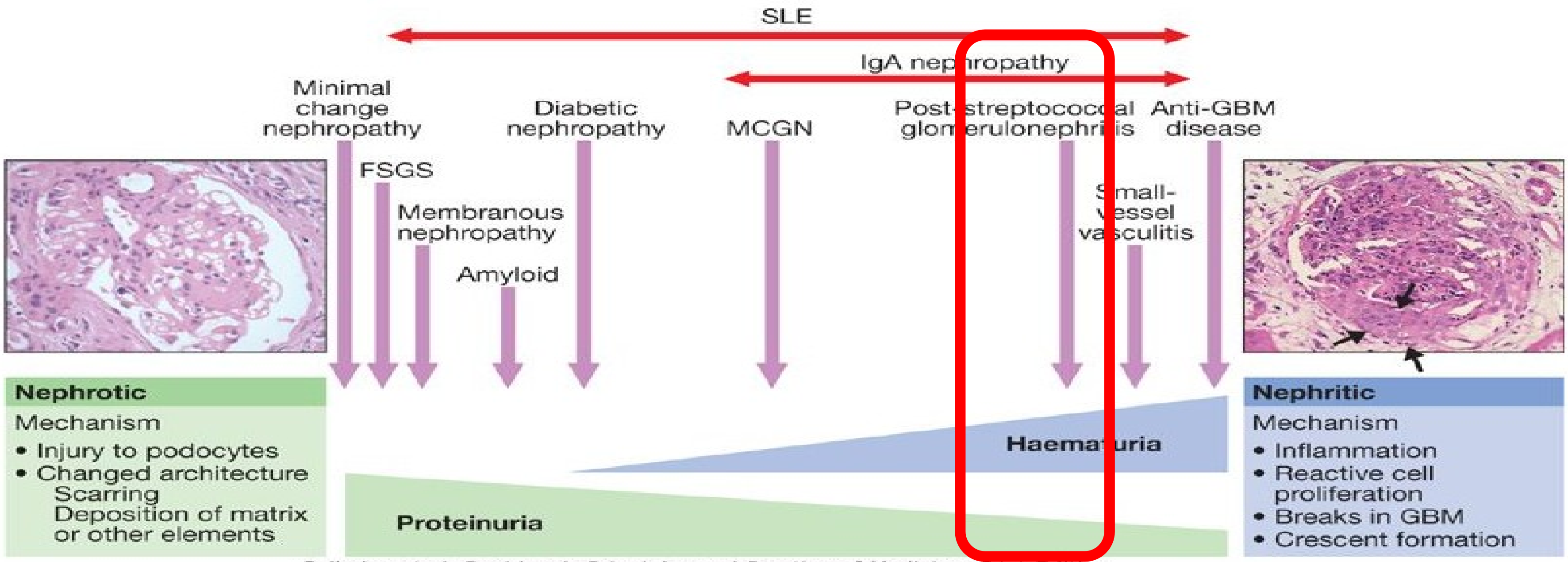
Time for Students' Questions

A 16-year-old female patient is referred from her GP with a four-day history of ankle and facial swelling and dark urine. Her last presentation at the practice was two weeks previously with pharyngitis. Blood pressure is 165/100 mmHg, and urine dipstick is strongly positive for protein and blood.

On admission she is in acute kidney injury with a creatinine of 1.9 mg/dl, renal ultrasound scan shows normal sized kidneys and no sign of obstruction.

What is your diagnosis?

Differential diagnosis of glomerular diseases



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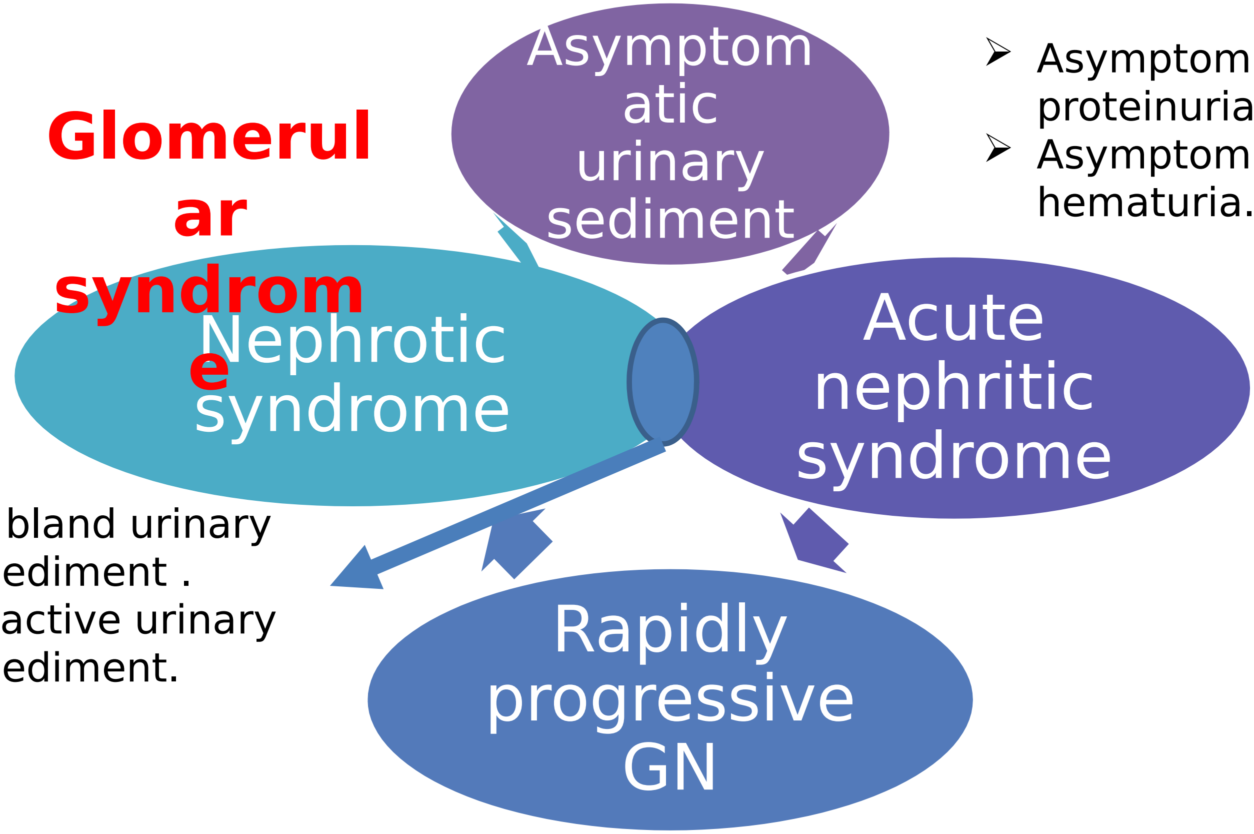
Clinical syndromes associated with glomerular diseases



Glomerular syndrome

Asymptomatic urinary sediment

- Asymptomatic proteinuria.
- Asymptomatic hematuria.

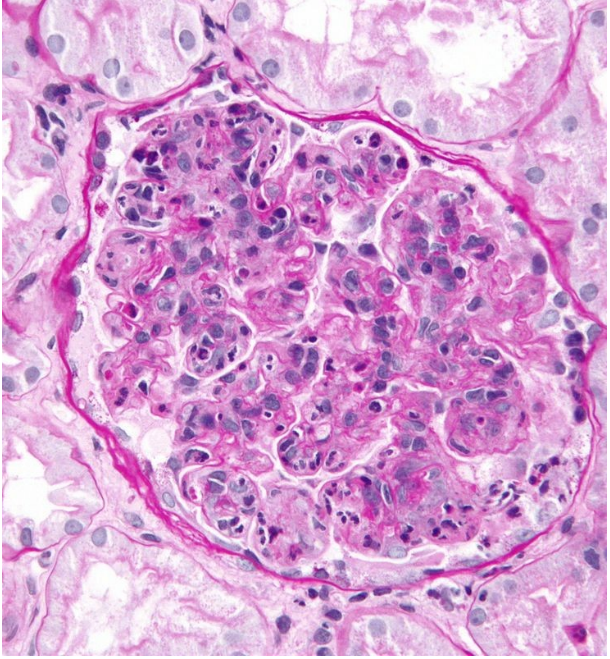
Nephrotic syndrome

Acute nephritic syndrome

- With bland urinary sediment .
- With active urinary sediment.

Rapidly progressive GN

Acute nephritic syndrome



- Is characterized by the abrupt onset (days) of:
  - Hematuria with RBC casts and/or dysmorphic RBCs.
  - Proteinuria (usually non-nephrotic range).
  - Altered renal function manifests (oliguria, a rise in blood urea nitrogen and creatinine, and/or retention of salt and water resulting in hypertension).
  - Most adults with acute nephritic syndrome require a kidney biopsy to establish the diagnosis

Differential Diagnosis of Acute Nephritic Syndrome

Serum complement

Low

- Post streptococcal GN
- OTHER Postinfectious GNs (e.g., bacterial endocarditis, shunt nephritis).
- Systemic lupus erythematosus (SLE).
- Membranoproliferative GN (MPGN).
- Cryglobulinemia

Normal

- IgA nephropathy
- Idiopathic rapidly progressive glomerulonephritis (RPGN).
- Anti-glomerular basement membrane disease (AGBM).
- Polyarterities nodosa.
- Wagner’s glomerulomatosis.
- Goodpasture’s syndrome.
- Henoch-Schnolein purpura.

Post-streptococcal glomerulonephritis (PSGN)

- PSGN occurs as a postinfectious complication of nephritogenic strains of group A β-hemolytic streptococcal infection.
- < 5% of those infected patient with pharyngitis is followed by PSGN within a 7- to 28-day latent period.
- 50% of infected individuals with Streptococcal pyoderma is followed by PSGN .
- PSGN is typically seen in children ages 3 to 12, although it can occur in adults.
- Both sexes are affected equally.
- More common in developing countries than industrial countries.
- PSGN occurs more frequently in the summer and autumn.

DIAGNOSIS of PSGN

Clinical findings of acute nephritis

Recent group A beta-hemolytic streptococcal infection

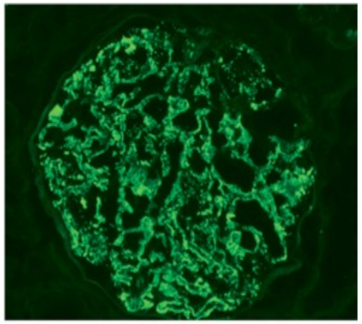
1. The clinical findings of acute nephritis.
1. On urinalysis :RBCs and RBC casts, white blood cells, and proteinuria.
2. A low serum complement (usually returning to normal at 6 to 12 weeks).
3. Azotemia.

Renal biopsy is not performed in most patients to confirm the diagnosis of PSGN.

a positive throat or skin culture

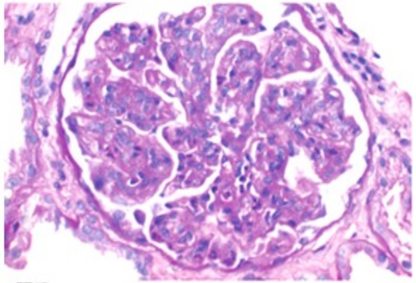
Antibodies to streptococcal antigens (ASOT).

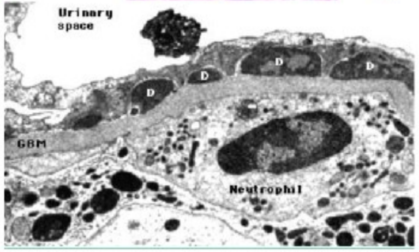
Post-streptococcal glomerulonephritis (PSGN)



Immunofluorescence demonstrating coarsely granular capillary loop deposits of immunoglobulin G.

Diffuse proliferative GN=diffuse proliferation and inflammatory cell infiltration





Subepithelial electron-dense humplike deposits by electron microscopy.

Treatment of PSGN

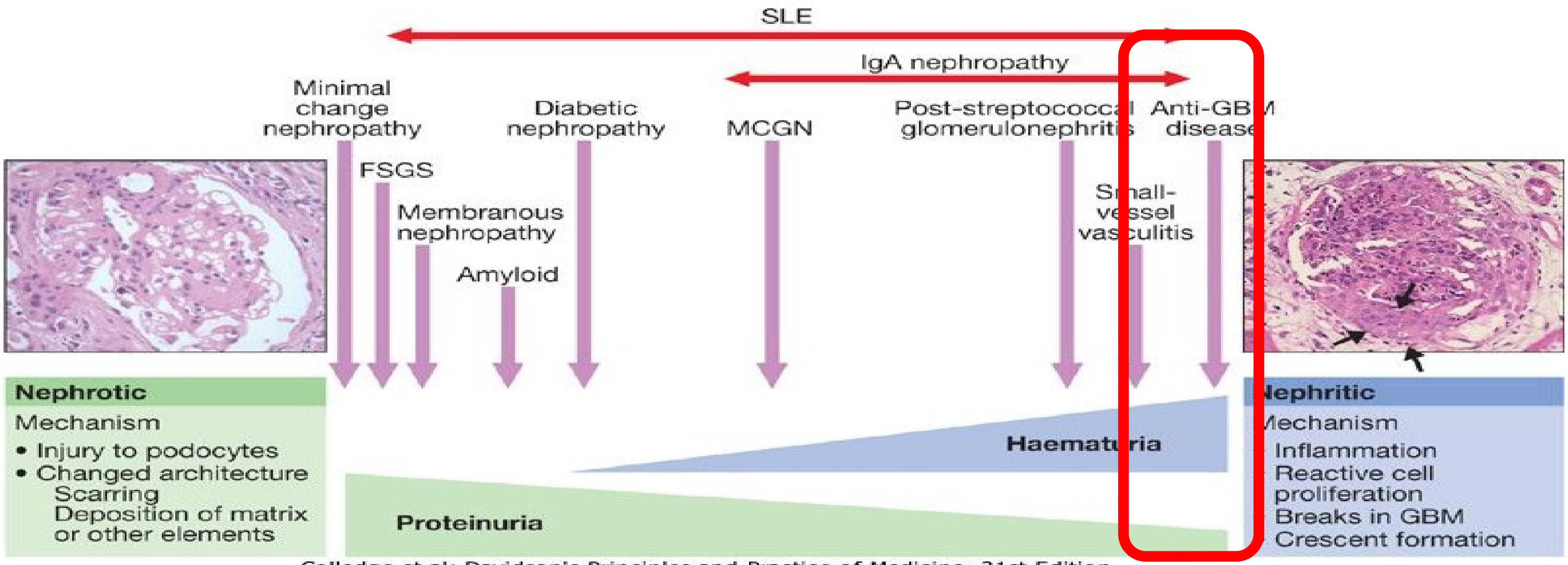
- There is no specific therapy for PSGN, although antibiotics should be administered if continued streptococcal infection is present.
- Salt restriction, diuretics and antihypertensive agents may be required to manage hypertension, edema, congestive heart failure, and other signs of sodium retention.
- Prognosis:
  - Complete recovery occurs in at least 90% to 95% of all patients.
  - Less than 5% of patients have oliguria for more than 7 to 9 days, and the prognosis in these patients is less favorable.
  - Proteinuria and/or hematuria may continue for 1 to 2 years in some patients.
  - Progression to chronic renal failure, though uncommon, is much more likely to occur in adults than in children.

How can post streptococcus GN can be presented?
How can you differentiate between post streptococcus GN and IgA nephropathy?

53-year-old man presents with massive hemoptysis.
He has been feeling generally unwell for a few days. He has started to become short of breath and has developed a cough productive of fresh blood.
His blood tests reveal:
Creatinine; 4 mg/dl. A urine dipstick reveals 2+ protein and 3+ blood.

How can you approach for this patient?

Differential diagnosis of glomerular diseases



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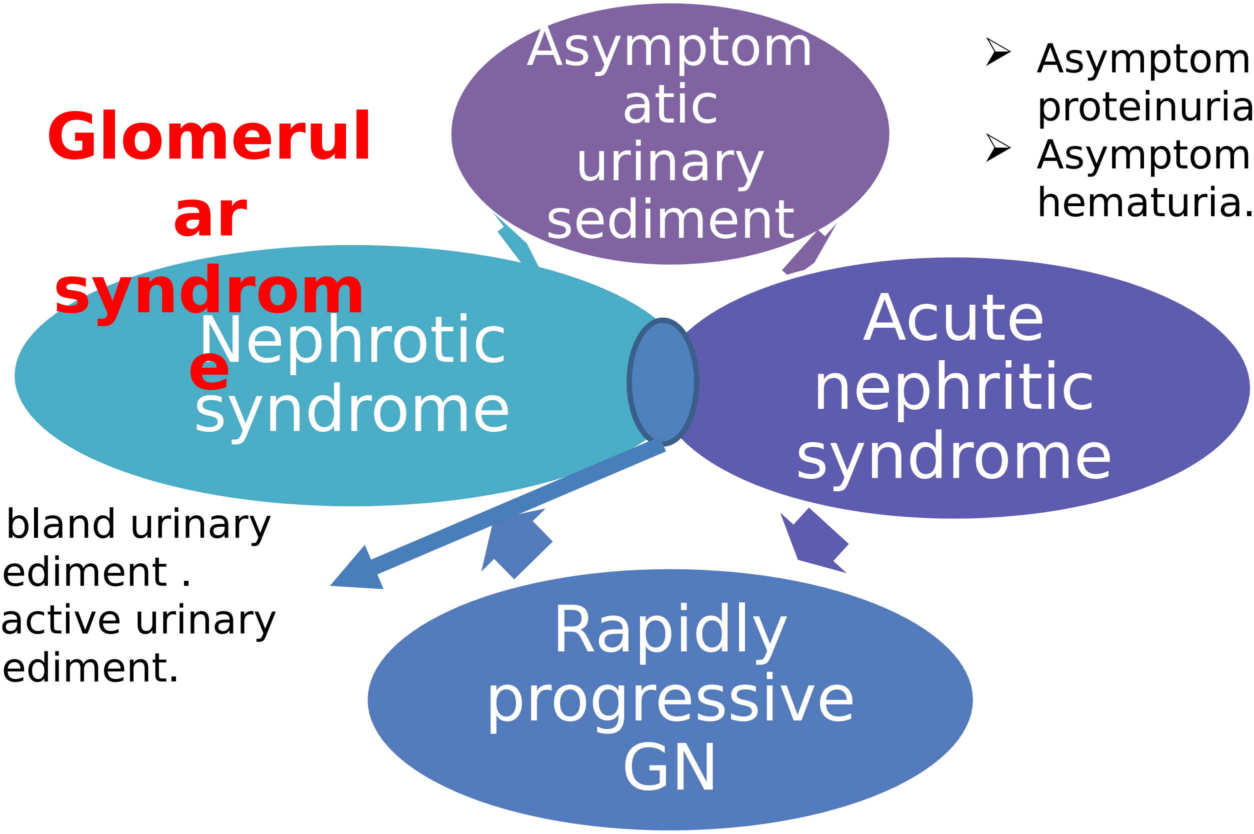
Clinical syndromes associated with glomerular diseases

Glomerular syndrome



Asymptomatic urinary sediment

- Asymptomatic proteinuria.
- Asymptomatic hematuria.

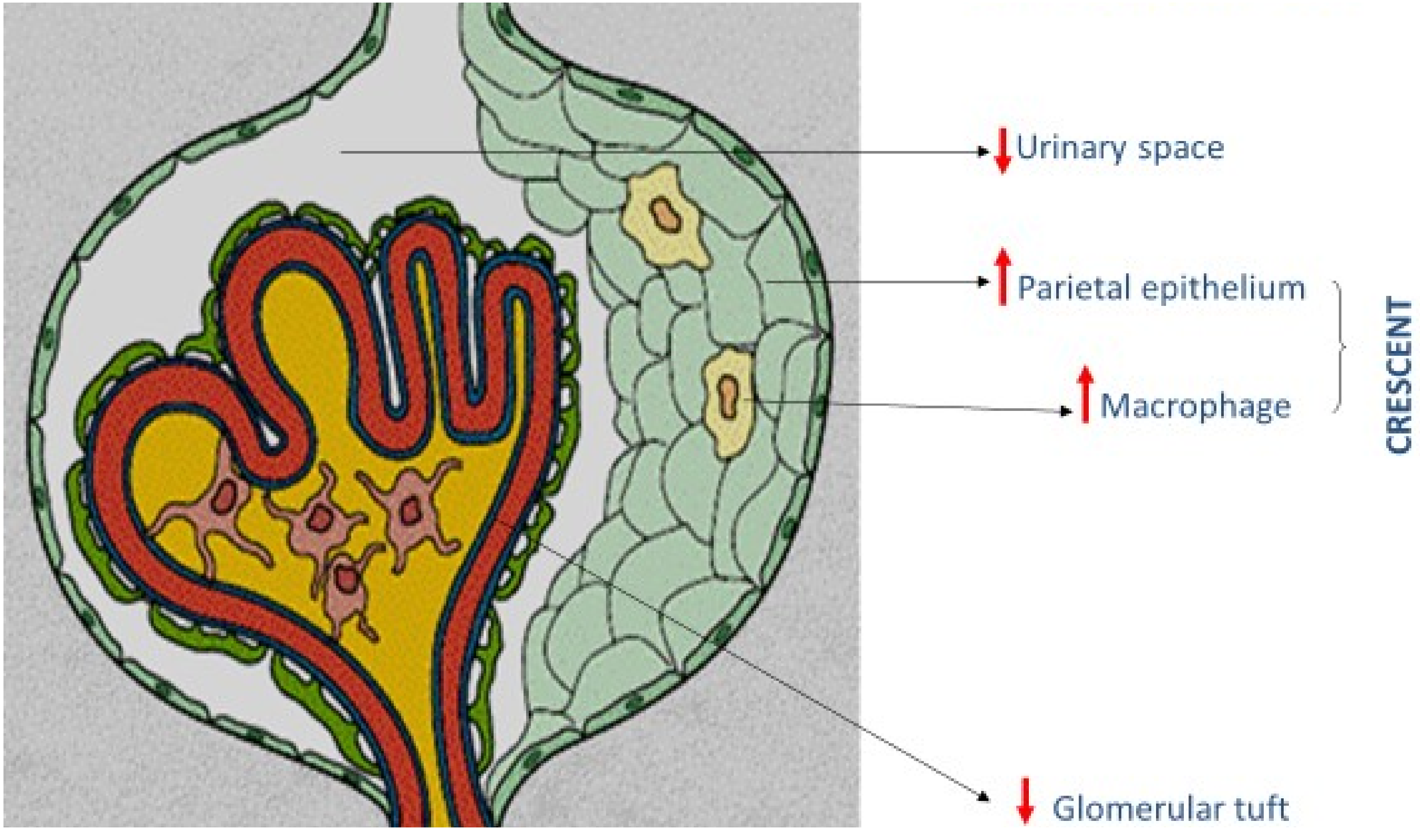
Nephrotic syndrome

- With bland urinary sediment .
- With active urinary sediment.

Acute nephritic syndrome

Rapidly progressive GN

Rapidly progressive GN



↓Urinary space

↑Parietal epithelium

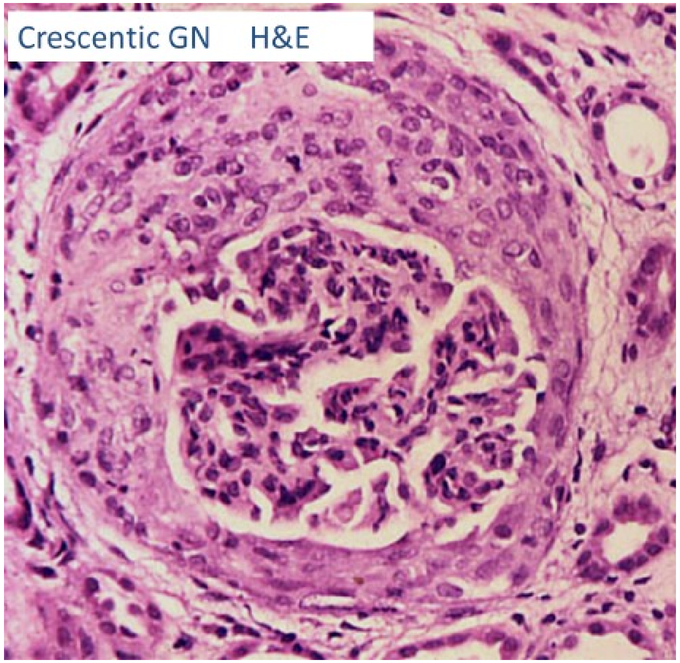
↑Macrophage

CRESCENT

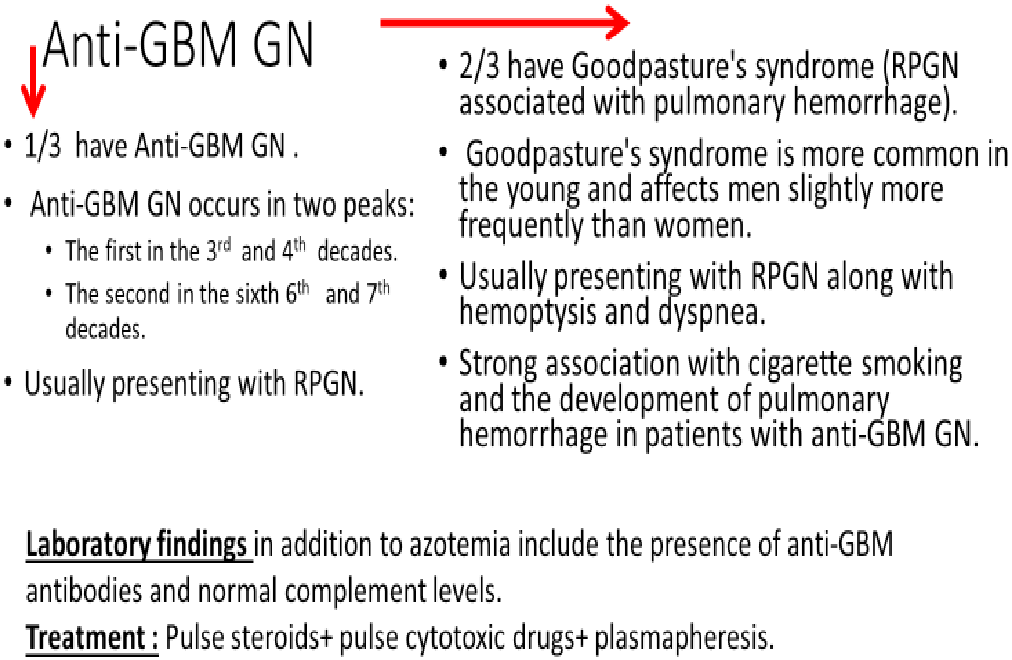
↓ Glomerular tuft

Rapidly progressive glomerulonephritis RPGN (crescentic GN)

- The term crescentic GN characterized by extracapillary proliferation (CRESCENT FORMATION evident on renal biopsy) in >50% of glomeruli
- Clinically presented by nephritic syndrome rapidly progressed (developing over *weeks to months)* to ESRD.
- The classification scheme is based on the IF formation obtained from renal biopsy.



Anti-glomerular basement membrane disease
Goodpasture syndrome



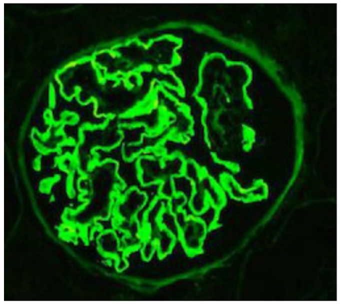
Anti-GBM GN

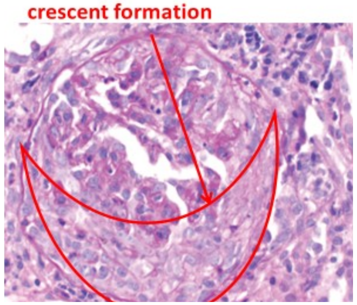
- 1/3 have Anti-GBM GN .
- Anti-GBM GN occurs in two peaks:
  - The first in the 3rd and 4th decades.
  - The second in the sixth 6th and 7th decades.
- Usually presenting with RPGN.

- 2/3 have Goodpasture's syndrome (RPGN associated with pulmonary hemorrhage).
- Goodpasture's syndrome is more common in the young and affects men slightly more frequently than women.
- Usually presenting with RPGN along with hemoptysis and dyspnea.
- Strong association with cigarette smoking and the development of pulmonary hemorrhage in patients with anti-GBM GN.

Laboratory findings in addition to azotemia include the presence of anti-GBM antibodies and normal complement levels.

Treatment : Pulse steroids+ pulse cytotoxic drugs+ plasmapheresis.





- Accounts for 10% to 20% of all cases of RPGN.
- Anti-GBM GN, characterized by extensive crescent formation and linear capillary loop staining with IgG and C3 by immunoflourescence.
- Clinically : RPRF , oliguria, hematuria (Dysmorphic RBCs), HTN.

Enumerate causes of RPGN.

Time for Students’ Questions

Quiz 1

- A 15-year-old man was seen at the clinic a week ago complaining of pharyngitis, and now returns because he has noted discoloration of his urine. He is noted to have elevated blood pressure (160/100 mm Hg) and urinalysis reveals RBC casts, dysmorphic RBCs, and 1+ proteinuria. Which of the following is the most likely diagnosis?

A. Systemic lupus erythematosus (SLE)
B. Amyloidosis
C. Post-streptococcal glomerulonephritis
D. Hypertensive glomerulosclerosis
E. Diabetic nephropath

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Quiz 2

- Which of the following is the best screening test for early diabetic nephropathy?

A. Random Urinary Albumin/ Creatinine Ratio
B. Dipstick urinalysis
C. Renal biopsy
D. Fasting blood glucose
E. 24-Hour urine collection for creatinine clearance

Quiz 2

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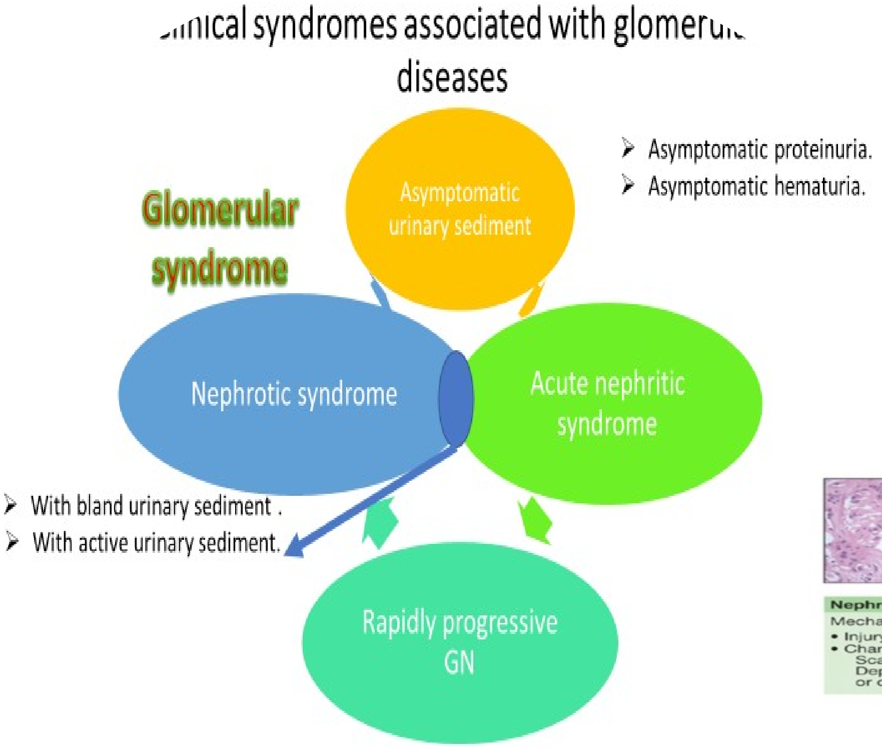
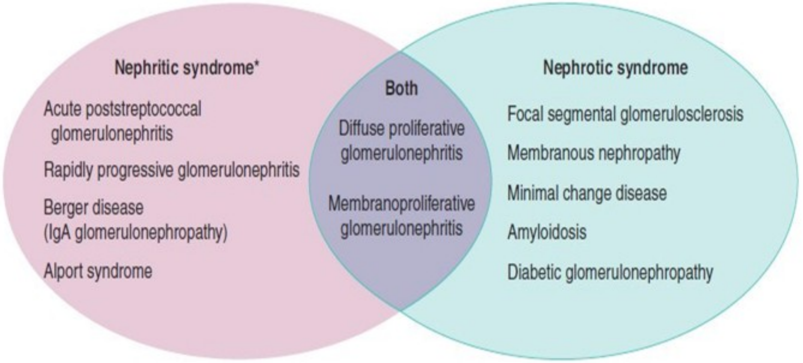
Remember glomerular syndrome



inical syndromes associated with glomeru
diseases

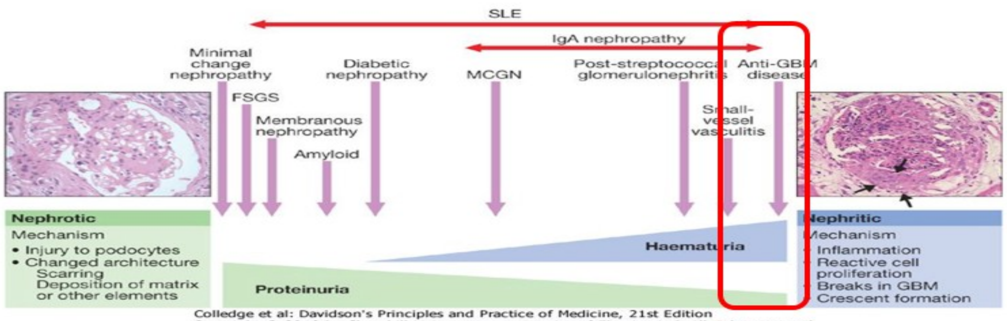
- Asymptomatic proteinuria.
- Asymptomatic hematuria.

- With bland urinary sediment .
- With active urinary sediment.



Nephritic syndrome*	Both	Nephrotic syndrome
Acute poststreptococcal glomerulonephritis Rapidly progressive glomerulonephritis Berger disease (IgA glomerulonephropathy) Alport syndrome	Diffuse proliferative glomerulonephritis Membranoproliferative glomerulonephritis	Focal segmental glomerulosclerosis Membranous nephropathy Minimal change disease Amyloidosis Diabetic glomerulonephropathy

Differential diagnosis of glomerular diseases



Nephrotic
Mechanism
- Injury to podocytes
- Changed architecture
  Scarring
  Deposition of matrix or other elements

ephritic
echanism
- Inflammation
- Reactive cell proliferation
- Breaks in GBM
- Crescent formation

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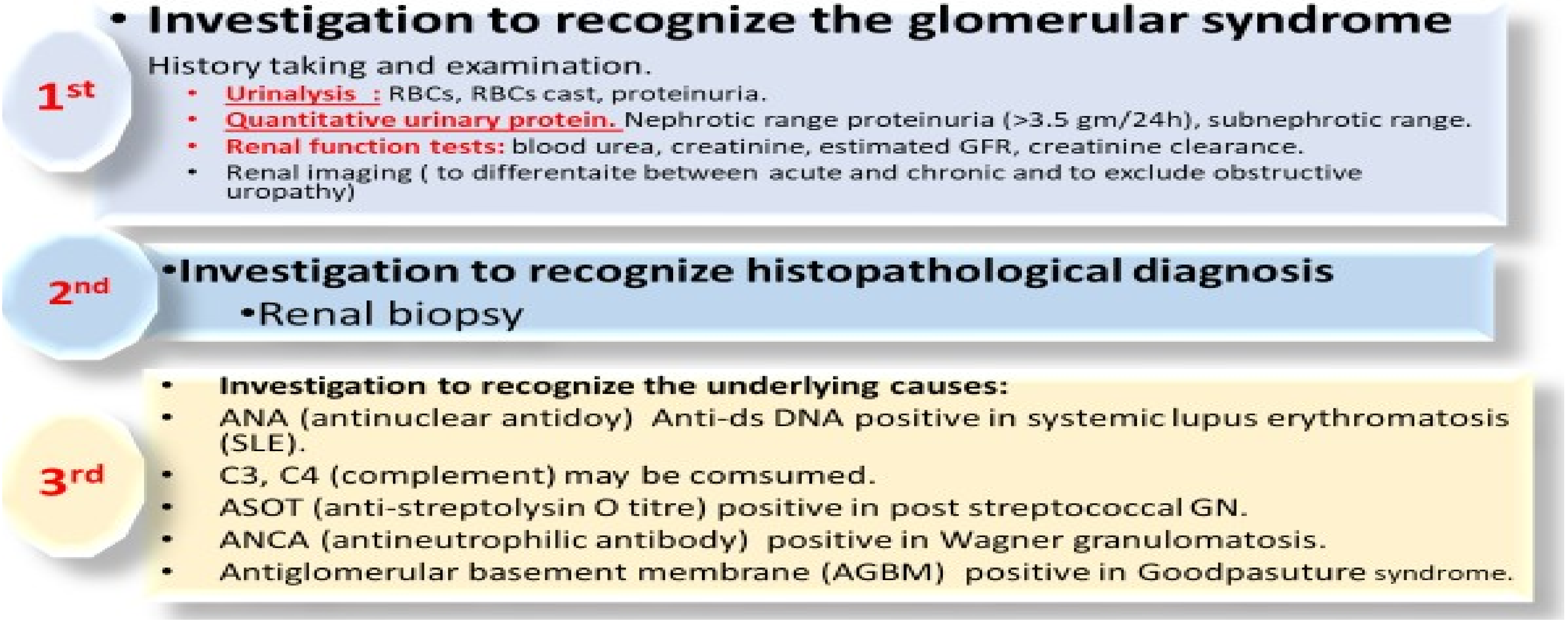
Diseases presented by either nephrotic and nephritic can be idiopathic or secondary to other causes.

Approach to patient with glomerular diseases



1st

- **Investigation to recognize the glomerular syndrome**

History taking and examination.

- **Urinalysis :** RBCs, RBCs cast, proteinuria.
- **Quantitative urinary protein.** Nephrotic range proteinuria (>3.5 gm/24h), subnephrotic range.
- **Renal function tests:** blood urea, creatinine, estimated GFR, creatinine clearance.
- Renal imaging (to differentaite between acute and chronic and to exclude obstructive uropathy)

2nd

- **Investigation to recognize histopathological diagnosis**
  - Renal biopsy

3rd

- **Investigation to recognize the underlying causes:**
- ANA (antinuclear antidoy) Anti-ds DNA positive in systemic lupus erythromatosis (SLE).
- C3, C4 (complement) may be comsumed.
- ASOT (anti-streptolysin O titre) positive in post streptococcal GN.
- ANCA (antineutrophilic antibody) positive in Wagner granulomatosis.
- Antiglomerular basement membrane (AGBM) positive in Goodpasuture syndrome.

Thank You